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Arena Pharmaceuticals, Inc.
Bozicevic, Field & Francis LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303

EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,955	CHEN ET AL.	
	Examiner	Art Unit	
	NIRMAL S. BASI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The GPCR of SEQ ID NO: 82 (TDAG8) defined in the instant application is supported by the parent applications 10/417,820 filed 4/16/2003 and 09/416,760 filed 10/12/1999. Based on an inspection of the parent applications, the examiner has concluded that the method of screening using the GPCR SEQ ID NO: 82 defined in this application is not supported by the disclosure in the other priority documents. Accordingly, the subject matter defined in claims 33-35 and 51-68 has an effective filing date of 10/12/1999.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 10/12/1999 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 10/12/1999.

2. Applicant has cancelled 1-68 and added new claims 69-87. Claims 69-87 are examined below as pertaining to the elected invention

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 33-35 and 51-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 76 is indefinite because it is not clear what biological response is detected so as to allow the metes and bounds of the claim to be determined.

Claim 79 is indefinite because of the use of "relative to" language when referring to P43A, K97N and I130F so as to allow the metes and bounds of the claim to be determined.

Claim 81 is indefinite because of the use of "relative to" language when referring to I225K so as to allow the metes and bounds of the claim to be determined.

Claim Rejections - 35 USC 101 and 35 USC 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Newly added claims 69-87 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. A specific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are

not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A well-established utility must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 69-87.

Applicant has not classified the GPCR TDAG8 of SEQ. ID. NO:82 into any specific family of GPCRs. The specification states:

"The present invention relates to a human T-cell death-associated gene receptor (TDAG8). The deletion of self-reactive immature T-cells in the thymus is mediated by apoptosis upon T-cell receptor interaction. Apoptosis is characterized by a rapid collapse of the nucleus, extreme chromatin condensation, DNA fragmentation, and shrinkage of cells, and it is often dependent on the synthesis of new sets of RNA and protein. (see, Choi et al., 168 Cellular Immun. 78 (1996)). There is a strong correlation between apoptosis and TDAG8; i.e., an increase in apoptosis results in an increase in the expression of TDAG8. Id. However, it is unknown whether an increase in TDAG8 expression causes T-cell mediated apoptosis, or if such expression is a result of such apoptosis. The endogenous ligand for TDAG8 is unknown and is thus considered an orphan GPCR having an open reading frame of 1,011 bp encoding a 337 amino acid protein. (TDAG8 was cloned and sequenced in 1998. Kyaw, H. et al, 17 DNA Cell Biol. 493 (1998); see Figure 1 of Kyaw for nucleic and deduced amino acid sequences.). Human TDAG8 is reported to be homologous to murine TDAG8. Human TDAG8 is expressed in the liver and in lymphoid tissues, including peripheral blood leukocytes, spleen, lymph nodes and thymus. TDAG8 is also reported to be localized to chromosome 14q31-32.1. Id."

The specification further discloses a human hTDAG8 with an I225K mutation which was shown to be constitutively active. The specification also discloses three other potential polymorphisms involving changes of amino acids 43 for Pro to Ala, amino acid 97 from Lys to Ans and amino acid 130 from Ile to Phe were cloned. Three is no disclosure that these three other potential polymorphisms contained active, inactive or constitutively active proteins.

The specification clearly states that the GPCR used in the claimed method is an **orphan receptor** with no known ligand. Further the cellular function of the orphan receptor is unknown. Although the orphan receptor has been isolated

along with four other potential polymorphs and experimentally studies to a certain degree, the specification sums up the state of the art as it pertains to TDAG8 or its mutants by stating: "**it is unknown whether an increase in TDAG8 expression causes T-cell mediated apoptosis, or if such expression is a result of such apoptosis.** In light of the specification the skilled artisan cannot come to any conclusions as to the function of the TDAG8 without further experimentation. The utility of TDAG8 cannot be implicated solely from homology to the proteins known in the art, from its expression pattern or its constitutive activation properties because the art does not provide the requisite teaching stating that all GPCRs have the same activity, same effects, bind the same ligands and are involved in the same disease states. No disease states or disorders are disclosed that are directly related to TDAG8 dysfunction.

The TDAG8 GPCR may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand characterized. The inclusion in the family of G protein coupled receptors (GPCR) does not constitute either a specific and substantial asserted utility or a well-established utility for that particular GPCR or protein. This is analogous to all proteins or GPCRs can be used as protein markers on a gel.

The specification discloses that TDAG8 is useful in screening, but the specification does not disclose what the claimed receptor specifically regulates and what specific disease the receptor is a target for. What would be the use of using the claimed receptor on a panel for drug screening? The receptor has no known ligand or known function. How would one use the compounds that interacted with said orphan receptors? It is unpredictable what ligands will bind to orphan receptors, and further the functional effects of ligand binding may remain uncertain even after extensive experimentation. What is the utility for a ligand, in many cases with no known function, that binds to a receptor of no known function? The ordinary artisan can only speculate on the utility for the ligand and receptor. A utility to orphan receptor cannot be assigned without

knowledge of what disease is associated with claimed receptor dysfunction or what drugs/ligands affect a specific claimed receptor function.

Knowing the tissue distribution of a GPCR and even its second messenger does not automatically mean that its function is known. **The family to which TDAG8 belongs is not disclosed. The specification discloses that ATP and ADP bind to TDAG8. The examiner has provided references where ATP and ADP can activate divergent GPCRs with no common utility. For example, Rhodopsin family of GPCR is by far the largest of the five human GPCR families and probably the most diverse based on it ligand specificity. Gloriam (Gloriam et al, Nine new human rhodopsin family G-protein coupled receptors, Biochimica et Biophysica Acta., Vol. 1722, pages 235-246, 2005) discloses many members of the Rhodopsin family can be activated by biogenic amines (such as adrenaline, dopamine, histamine and serotonin) and peptides (such as angiotensins, bradykinins, omatostatins, melanocortins, opioids, and galanin). Rhodopsin GPCRs can also be activated by large proteins (such as LH, FSH and TSH), nucleosides and nucleotides (such as adenosine, ATP, UTP and ADP), lipids and eicosanoids (such as eukotrienes, prostaglandins, cannabinoids and free fatty acids) and photons. Moreover, the large group of olfactory receptors belong to this family but two thirds of the 900 genes for olfactory receptors are pseudogenes in humans. Only a few members within this subgroup are characterized with regard to ligand specificity and hence the majority of olfactory receptors are orphans. The therapeutic potential of most members in this group has, however, not yet been exploited as many of these receptors are still orphans, without known ligand or physiological function. The showing of a relationship to other GPCRs does not necessarily mean that the biological function or ligand can be determined without extensive experimentation. Gloriam discloses GPR72 is expressed in regions of the hypothalamus, hippocampus and amygdala in both rodents and humans. GPR72 was previously suggested to be a new NPY**

receptor but experiments showed that it does not bind NPY-receptor ligands in standard binding assays and this receptor is still an orphan GPCR. Therefore tissue specificity can sometimes be meaningless as it pertains to determining physiological function or dysfunction. Gloriam discloses that the previously orphan GPCRs, GPR40, GPR41 and GPR43 were found to be low affinity receptors to free fatty acids. These receptors have fairly low similarities to other GPCRs and many of their closest relatives bind peptides, except those that bind leukotrienes (the BLTR receptors).

Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Murdoch et al (Blood, Volume 95, No.10, pages 3032-3043, 2000), in the discussion of cytokine G-protein-coupled receptors. The utility of TDAG8 cannot be implicated solely from homology to known G-protein coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. Further, the specification does not appear to have used protein domains/homology to predict the activity of the protein. Murdoch discloses the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Watson (The G-Protein Linked receptor Facts Book, pages 2-6 and 223-230, 1994) states ."**it has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence"**. Therefore the disclosure of Watson predicts, using the primary structure of the G-protein coupled receptor the skilled artisan cannot predict its associated G-

protein or its ligand. G-protein coupled receptors are highly specialized and ligand specific proteins. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with alkaloids, biogenic amines, peptides, glycoprotein hormones, light and odorants (Terry Kenakin, Pharmacological Reviews, Vol. 48, No.3, pages 413-462), see page 413. Kenakin also states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) **"In-depth analysis of protein sequences often results in functional predictions not attained in the original studies"**, page 313, column 2, last paragraph, d) **"However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy**

from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and **"Today, what we predict from sequences is at best fragmentary and qualitative"**, page 332, column 2, second paragraph.

Based on the art, the limited homology of claimed GPCR to other proteins cannot be used to predict its function. The following articles are also cited as evidence for the unpredictability of determining a function or ligand of TDAG8

based on homology of GPCRs. Further there is the even greater unpredictability of using TDAG8 to treat a disease related to TDAG8 dysfunction.

Civelli et al (Civelli et al, Pharmacology and Therapeutics, November 8, pages 1-8, 2005) discloses that all 7 transmembrane receptors are not GPCRs (page 2, column 1). GPCRs are activated by a plethora of transmitters and have a broad spectrum of interactions. **The role of GPCRs in various tissues may be different although the second messengers that result from its initial activation are probably the same.** Most GPCRs started as orphan receptors and the discovery of new members found by homology screening suffers from one obvious problem, the receptors found lack their pharmacological identities, their natural ligands (gage 2). **The pursuit to unravel their identities has led to fishing expeditions. The number of orphan GPCRs has steadily increased and at this time the GPCRs outnumber the known potential ligands.** Researchers utilize orphan receptors as baits to isolate their natural ligands, which is meant to identify novel transmitters (page 3). Civelli also discloses the discovery of the natural ligand is no easy task, and specifically states, "GPCRs have been depolarized at a rate of 7-8 per year from 1999 until 2004. This was mostly the result of large-scale random screening of practically all molecules known to exist in cell", (page 4, column 2). There is no rule for predicting the affinity constant of a natural ligand at a particular receptor. The level of receptor expression in a transfected cell can affect ligand potency and is subject to artifacts. Belonging to a family of GPCRs does not insure that all members will bind the same ligand or have the same effects. The recently discovered Mas-related GPCRs, orphan receptors, bind a variety of structurally divers transmitters (ligands), Rfamide peptides for some mouse Mrgs and cortistatin for two human Mrgs, adenine for rat Mrg and beta-alanine for an Mrg found in human, rat and mouse (column 2, page 5). The matched transmitters are specific to particular Mrgs and activate them efficiently. By the mid-1990s approximately 90 transmitters were known, since then, a dozen new transmitters have been found and it is expected that the remaining 120 orphan GPCRs will

lead to the discovery of at least 50 more transmitters (page 6, column 1). **There is no doubt that orphan GPCRs are used as potential drug targets but there is no marketed drug directed at any of the ones that have been depolarized since 1995** (page 6, column 1). **Many targets even when recognized of therapeutic interest have showed no value for drug screening** (table 2).

Hancock (Hancock, A.A., Biochemical Pharmacology, Vol. 71, pages 1103-1113, 2006) discloses although histamine H3 receptor (GPCR) was identified pharmacologically in 1993, and despite widespread pharmaceutical interest in the target, no compound interacting specifically with this site has undergone successful clinical examination to develop the necessary proof-of-concept data. The pharmacological effects of known H3 ligands are complex and diverse, since these agents may act both as agonists and antagonists in different systems. Moreover, other compounds show inverse agonism in some models but neutral antagonistic activity in others (see abstract).

Feng et al (Feng et al., Kidney Research, May, Vol. 67, Issue 5, pages 1731-1738, 2005) discloses the heterogeneity for a GPCR AT2 receptor in both ligand binding and induction of arachidonic acid release. The AT2 receptor exhibits distinct biochemical and biological properties compared to its highly homologous orthologues (91% homologous in overall amino acid sequence) of rat, mouse and human. The reducing agent DTT inactivates the rabbit othhologue but potentates the others in ligand binding. Rabbit AT2 receptor but not the other orthologues, induces arachidonic acid release in various cell systems when stimulated with Ang II and CGP42112A, the peptide antagonist. Mutagenesis studies and sequence analysis further indicate that residues His106, ASP188 and Thr393 are responsible for DTT inactivation and residues Val209 and Val249 are partially responsible for arcchidonic acid release (see Abstract)

Marchese et al (Marchese et al., TIPS, Vol. 20, pages 370-375, September 1999) discloses the search for novel GPCR genes (cloning by low stringency hybridization to cDNA/genomic DNA libraries) has far outpaced the

identification of novel endogenous ligands, more than 80 orphan GPCRs are awaiting a ligand. Many orphan GPCRs are found to be similar to known GPCRs. Where the identity reaches the threshold of approximately 45% it is likely that the receptors will share a common ligand but **this rule is not without exception** (page 371, column 1)). For example the orphan RQ/nociceptin receptor (has approximately 65% amino acid identity to opioid receptors but does not have high affinity for opioid peptides**). Many GPCR subtypes have less than 40% amino acid identity, in which case sequence comparison might not be profitable.** Moreover because the ligand-binding pocket has not been described fully for any receptor, it is not feasible to predict ligand identity. There are no signature amino acids that predict either the nature of the ligand or the identity of the interacting Galpha subunit type(s) (page 371). **Further, the elusive nature of certain labile natural agonists could be a significant hindrance to the discovery of orphan ligands, as there is no reason to believe that the remaining orphan GPCR ligands will all prove to be peptides.** Recently, new complexities have added to the general approach to studying orphan GPCRs. The efficient binding of a ligand to the receptor may require the co-expression of a co-factor protein, e.g. receptor activity modifying protein 1 (RAMP1) in case of amylin binding to orphan GPCR calcitonin receptor-like receptor. Heterodimerization of two subunits may be required for formation of a functional receptor, e.g. GABAb receptor (page 374). The characterization of some GPCR might be more complex than expected, perhaps indicating that functional assays should begin to include co-expression of related orphan GPCRs.

Vanti (Vanti et al., Biochemical and Biophysical Research Communications, Vol. 35, pages 67-71, 2003) discloses the **sequence of a receptor does not necessarily provide insights into the nature of its cognate ligand and therefore such receptors are termed orphan GPCRs**. Vanti, further discloses while some GPCRs, e.g. GPR133 and GPR134, may be nearly identical (95%) they are expressed in different CNS tissues suggesting

that this family of receptors may have diverse roles in the CNS (page 70, column 1). Further Vanti discloses the efforts to identify and catalog all human GPCR-encoding genes are ongoing, and these efforts have resulted in the identification of entirely novel signaling systems such as apelin, melanin-concentrating hormone, metastin and urotensin (page 70, column). Based on Vanti's observation it is highly possible that the claimed GPCR may signal through a novel signaling system. The claimed receptor, based on the preceding references could also have a novel natural ligand that as of yet, has not been identified or purified.

Mutations in a receptor can affect function. Vanti et al (Vanti et al., Genomics 82, 531-536, 2003) discloses that null mutations can arise in a GPCR that renders it truncated and non-functional). Therefore, in the case of the Vanti variant the wrong probe would not detect anything. The GPCR may also be present in other tissues than indicated. The method used of detection is very important. For example, Ta-Tung (Ta-Tung et al, Gene, Vol. 278, pages 41-45, 2001) discloses the assay and tissue used is very important in determing the information gleaned. Ta-Tung discloses (page 49, column 2) that although PSGR (a GPCR) RNA could not be detected by northern analysis in total RNA from whole brain tissue, RT-PCR analysis of five human brain tissue analyses of five regions did reveal the presence of PSGR mRNA specifically in the olfactory epithelium and medulla oblongata (Fig. 3). Based on the wide spread distribution of claimed polynucleotide there is insufficient information provided on which to base a utility of using GPCR 16405 as a marker for a disease state.

Further, the ability of a GPCR to increase second messenger levels of a compound (e.g. calcium, IP3) by interaction with a G protein in a specific cell type does not mean all GPCRs will have the same physiological function. Even if a GPCR (with known function) increases second messenger levels, for example IP3 levels, in a specific cell, the art discloses that another receptor, which also affects IP3 levels, may have a completely different biological function. Cells are exposed to many extracellular stimuli, yet they respond appropriately only to

specific signals, often by means of just a handful of intracellular messengers. There is more to specificity than the controlled expression of signaling proteins. Taylor (Taylor et. al., Calcium signaling:IP3 rises... and again, Current Biology, Vol. 11:R352-R353, 2001), discusses these issues at length and state," **Even within a single cell, different receptors may use the same intracellular messenger molecule to very different effect**", page R352. The ability of GPCRs to interact with other proteins in the cell and the effect of feedback mechanisms allow them to use the same proteins, e.g. Gq proteins in the case of IP3, or second messenger pathways but have very different effects. For example, Taylor (page R352, column 2) discloses that in pancreatic acinar cells cholecytokinin and acetylcholine receptors use the same Gq proteins to stimulate phospholipase C and so trigger Ca2+ release from intracellular stores, yet the patterns of Ca2+ signals they evoke are quite different". Such diversity sits uneasily with mechanisms wholly dependent on Ca2+ regulation of IP3 receptors. The diversity of signal transduction also applies to receptor subtypes. For example, stimulation of one subtype of metabotropic glutamate receptor, mGluR5, evokes Ca2+ spikes via IP3, but stimulation of another subtype expressed in the same cell, mGluR1 depends upon a single Ca2+ transient. The difference depends upon a single PKC phosphorylation site in mGgluR5 (see Taylor, page R354, column 1). The versatility of the signaling mechanism in cells is also discussed by Berridge et al (Berridge et al, The versatility and universality of calcium signaling, Nature Reviews Molecular Cell Biology, Vol. Pages 11-21, 2000). Berridge discloses the versatility of the signaling mechanism is enhanced by having different second messenger mobilizing molecules linked to separate input signals. Therefore in a given cell two separate molecules linked to the same second messenger such as IP3 can have different effects on the cell.

Han (Han et all, Genomics, 87, pages 552-559, 2006) discloses changes in cell (293 cells are human embryonic kidney cells) culture conditions influence the metabolism of cells, which consequently affects the quality of the products

that they produce such as recombinant proteins. Depending on the confluence status of the cells certain genes can be up or down regulated (see page 557, column1). In instant case there is no disclosure of the level of transfection or the amount of recombinant protein produced by the cells expressing claimed invention. Even if second messeneger is identified that is affected by applicants invention the increased/decreased second messenger levels may be due to over expression/under expression and have nothing to do with the natural state of the cells in the native tissue as it pertains to expression and second messenger effects of claimed receptor.

Susens et al (Neuropharamocology, Vol. 50, pages 512-520, 2006) discloses GPR139 was exclusively expressed in the brain and was present strongly in E15 and E17 and very weakly in E11 embryos (Fig. 2A). Two human brain-specific northern blots were assayed with a probe covering nucleotides 295–1035 of mouse GPR139 and showed predominant expression in putamen, medulla and caudate nucleus. Weaker signals were present in thalamus, amygdala, and spinal cord. In instant application the specific regions of the brain expressing GPCR 16405 are not disclosed, therefore, making it even harder to predict function. The type of cell and the GPCR expressed is very important to the effect observed. Susens, discloses, stable expression of GPR139 and another related GPCR, GPR142, was established in the flip-in cell lines CHO-K1 and HEK-293. In both stable cell lines GPR139 was more strongly expressed than GPR142, as shown for CHO-K1 cells in Fig. 6A–F. In HEK-293 cells GPR139 appeared as monomer and in CHO-K1 cells as dimer (Fig. 6G, middle panel). This indicates that a partner or conditions are present in CHO-K1, but not in HEK-293 cells, which favor dimer formation and potential functions. Susens, discloses, “To analyze possible ligands we concentrated on GPR139 because of its higher protein-expression levels and better presentation at the outer cell membrane.” Susens shows that the effect of certain effectors in brain extract used to stimulate GPR139 is predominantly mediated by an inhibitory G-protein. Susans concludes by suggesting, “The

presence of GPR139 in brain areas involved in motor control suggests a function as mediator in locomotor activity. Identification of a ligand or of ligands for both receptors may help to clarify their function." Even after disclosing a very specific pattern of distribution the function of the GPR139 still needs to be clarified. In instant, during the course of experimentation to determine receptor activity and physiological function the type of cell used will influence the results obtained. The problem could be further compacted if the claimed receptor needs to be present as a dimer to function naturally.

Gloriam et al (Biochimica et Biophysica Acta, Vol. 1722, pages 235-246, 2005) disclose GPR139 has a very restricted expression pattern and perhaps reflecting that its functional role is more cell-specifc and/or that the expression levels are low. Lower expression levels would suggest lower IP3 levels in the brain. This leads to the question does the artisan activate or inhibit GPCR 16405 to correct a specific disorder or dysfunction. What ligands will the artisan use to correct this defect, none are known in the art and none are disclosed in the specification.

Therefore the experimental design and the cells used to analyze the GPCR activity greatly influence the results obtained and therefore cast doubt on the interpretation of the results. Further there is nothing in the specification or prior art that suggests that the claimed isolated GPCR encodes a dysfunctional polypeptide that when stimulated or inhibited will correct a disease state. This means that the artisan still has to do further research to determine if claimed GPCR is the product of a dysfunctional gene and what association, if any, it has with a specific disease state.

Lee et al. (Expert Opin. Ther. Targets, Vol 6(2), pages 185-202, 2002) discloses one of the most important tasks of modern pharmacology lies in elucidating the functions of GPCRs. Of particular interest are receptors with recognized expression in the central nervous system. Lee also discloses, "The investigation of the physiological and molecular mechanisms of any signal transduction system requires the identity of both ligand and receptor. For this

reason, characterization of oGPCRs remains limited until discovery of their endogenous ligands. Prior to discovery of apelin, the apelin receptor was known to be expressed in the CNS and in the periphery, being especially abundant in developing cardiovascular systems with an additional role as a HIV coreceptor in vitro. However, the physiological roles of the receptor were still undetermined for many years. With the identification of the apelin peptide, there is now evidence of several physiological functions, including the modulation of blood pressure, drinking behavior and immune system function" Lee also discloses many examples where the GPCR and its associated G protein are known, therefore the second messenger is also known but extensive experimentation still is required to discover a physiological function. Lee further highlights the problem of assigning function based on tissue specificity by the example on page 194. Lee discloses there remain several somatostatin-like (and closely-related opioid-like) oGPCR, which have yet to be paired with an endogenous ligand. The genes encoding the oGPCRs named GPR7 and GPR8 were both discovered in 1995, shown to be expressed in rat brain in 1999 (GPR7 and GPR8 are both expressed in discrete regions of the brain and GPR8 appears to be species specific, i.e. absent in rodents) did not bind opioid receptor sub-type-specific compounds or somatostatin. The Lee article was published in 2002, seven years after the discovery of GPR7 and GPR8. Another oGPCR, SALPR, expressed in the brain, particularly in the substantial nigra and pituitary, with some expression in the periphery awaits the identification of its specific endogenous ligand. Therefore determing the physiological function of a GPCR and its endogenous ligand is no easy task, even knowing its tissue specificity.

Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of GPCRs, which have very different ligand specificity and functions. The discovery of the endogenous ligands will help determine the precise physiological role for each orphan GPCR. As the functions of these novel receptors are uncovered, they could become targets for the development

of new pharmacological therapies for diseases not previously considered amenable to pharmacological therapy, but this requires further research and therefore the invention is not complete.

It can be argued the TDAG8is a useful tool as a reagent or a molecular target in the diagnosis and treatment of GPCR mediated disorders. All members of the GPCR protein family have a utility in selectively screening of candidate drugs that target GPCRs. However, for a utility to be well established it must be specific, substantial and credible. In this case, the particulars of screening of candidate drugs, that target GPCR of SEQ ID NO:56, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to GPCR of SEQ ID NO. Because of this, such a utility is not specific and does not constitute a well-established utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the TDAG8 for screening compounds that are a target for the GPCR is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the GPCR family. Again, this is a utility, which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual GPCR is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using claimed GPCR has no well-established use. The artisan is required to perform further experimentation on the claimed GPCR itself in order to determine to what use any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a protein/polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the TDAG8 and a disease or disorder. The presence of TDAG8 in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed GPCR and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow TDAG8 to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the TDAG8 is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of TDAG8 as a diagnostic for a disease. However, in the absence of any disclosed relationship between TDAG8 and any disease or disorder and the lack of any correlation between the claimed GPCR with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, TDAG8 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities

due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the GPCRs has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed GPCR, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by the GPCR family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ

1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:82 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of TDAG8. Applicant has failed with respect to GPCR TDAG8, has not described the family of GPCRs in enough detail to show, by a preponderance of the evidence, that TDAG8 has any substantial use. The record shows that the family of proteins having GPCR domains is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. The use of the claimed invention for screening assays, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that TDAG8 might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the

disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.)

The rejection under 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

5. Claims 33-35 and 51-68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the TDAG8 GPCR further experimentation is necessary to attribute a utility to the claimed invention.

Claim Rejection 35 USC 112, 1st paragraph (Written Description)

6. Claims 69-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 69-87 are drawn to use of a GPCR that can bind agonist and alter cAMP levels in a cell, wherein the GPCR comprises an amino acid sequence that is at least 80%, 95% or 99% identical to the amino acid sequence of SEQ ID NO:82;

The claims do not require that the polypeptide possess any particular GPCR related activity. There is also no requirement that any particular domains shown to be essential for activity be maintained. Although some claims require that a specific mutation be made, but this in the absence of other functional domains of the GPCR are meaningless as it pertains to making functional molecules. Although applicant has shown variants of TDAG8, they only vary by one amino acid. Of the variants shown only the I225K mutation has been disclosed to be active, i.e. endogenous ATP and ADP result in an increase of at least 110% in cAMP level in CRE-LUC cell or 130% in CRE-293T cells. TDAG8 variants containing mutations at positions 43, 97 and 130 of the polypeptide disclosed SEQ ID NO:82 have been disclosed but there is no indication that they are active. There is no indication that they bind the same ligand or even have the same activity as the I225K mutation. As seen by the I225K mutation of TDAG8, the type of mutation as well as the cell it is expressed in determines the effect of compounds on it's functionality and inturn its effect on other signaling pathway compounds. A mere statement that TDAG8 is merely 80% or 95% identical is insufficient to meet the written description requirement for the use of TDAG8 variants in instant case. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

The amino acid sequence of orphan TDAG8 is disclosed in SEQ ID NO:82 but the specific activity, associated function and activating ligands have not been

disclosed. The specification and the prior art do not provide a specific assay for the claimed genus of polypeptides. The superfamily of GPCRs are specialized proteins designed for chemical recognition of specific ligands and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. GPCRs interact with many diverse compounds having diverse effects. The important features which would help to define the TDAG8 activity and define the genus claimed have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

Claimed GPCR is stated to belong to the family of GPCR, the specific family is not disclosed. The Rhodopsin family is by far the largest of the five human GPCR families and probably the most diverse based on it ligand specificity. Gloriam (see above) discloses many members of the Rhodopsin family can be activated by biogenic amines (such as adrenaline, dopamine, histamine and serotonin) and peptides (such as angiotensins, bradykinins, omatostatins, melanocortins, opioids, and galanin). Rhodopsin GPCRs can also be activated by large proteins (such as LH, FSH and TSH), nucleosides and nucleotides (such as adenosine, ATP, UTP and ADP), lipids and eicosanoids (such as eukotrienes, prostaglandins, cannabinoids and free fatty acids) and photons. Moreover, the large group of olfactory receptors belong to this family but two thirds of the 900 genes for olfactory receptors are pseudogenes in humans. Only a few members within this subgroup are characterized with regard to ligand specificity and hence the majority of olfactory receptors are orphans. The therapeutic potential of most members in this group has, however, not yet been exploited as many of these receptors are still orphans, without known ligand or physiological function. The showing of a relationship to other GPCRs does not necessarily mean that the biological function or ligand can be determined without extensive experimentation. Gloriam discloses GPR72 is expressed in regions of the hypothalamus, hippocampus and amygdala in both rodents and humans. GPR72 was previously suggested to be a new NPY

receptor but experiments showed that it does not bind NPY-receptor ligands in standard binding assays and this receptor is still an orphan GPCR. Therefore tissue specificity can sometimes be meaningless as it pertains to determining physiological function or dysfunction. Gloriam discloses that the previously orphan GPCRs, GPR40, GPR41 and GPR43 were found to be low affinity receptors to free fatty acids. These receptors have fairly low similarities to other GPCRs and many of their closest relatives bind peptides, except those that bind leukotrienes (the BLTR receptors). In instant case the ligand that binds to claimed receptor is not known, physiological function is not known and the second messenger is not known.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a polypeptide, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the polypeptide has been isolated. Thus, claiming all polypeptide that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad % in relationship between the claimed polypeptide sequence, either in terms of its amino acid sequence and the single

disclosed species of SEQ ID NO:82. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of polypeptide sequences that are at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also contain a polypeptide with an undisclosed GPCR activity. The fact remains that the actual polypeptide with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature or contained a specific GPCR activity. All GPCR activities are encompassed by the claims. There is no disclosure of how to make a polypeptide, or even an example of a polypeptide having an amino acid sequence having at least 95% identity with the amino acid sequence of SEQ ID NO:82, wherein the polypeptide has the functional properties of GPCR TDAG8. Returning back to percent identity (homology), to put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and

the reference sequence are substitutions, can be calculated by the following formula:

$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 95% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300 nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:82 is 337 amino acids long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 95% identical to the reference amino acid sequence, would be a very, very large number. While limiting the scope of potential sequences to those that are at least eg 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of

impossibility of making and testing sequences for those, which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. As disclosed by the references above the functionality of the GPCR cannot be predicted from sequence comparisons of the polypeptide of SEQ ID NO:82 with those in the known art. A single point mutation may have a dramatic effect on the properties of the GPCR. The specification also provides no teachings on what 20% or 5% amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active claimed isolated polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have sufficient structural homology with SEQ ID NO:82 to predict functional activity, it is not possible to even guess at the amino acid residues, which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in case to case painstaking experimental study to determine active variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary amino acid sequence derivatives encoding a biologically active polypeptide with an amino acid sequence differing from SEQ ID NO:82 as claimed since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:82, for a polypeptide having the necessary properties for the disclosed uses, and provides four point mutation variants, only one of which has been shown to be active and no guidance on obtaining functional polypeptide variants of SEQ ID NO:82 with 80% or 95% which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description" inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the ad to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:82 but not the full breadth of the claims meets the written description provision of 35 U.S.C.112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIRMAL S. BASI whose telephone number is (571)272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nirmal S. Basi/
Examiner, Art Unit 1646

/Michael Pak/
Primary Examiner, Art Unit 1646